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Participation of the Thalamic CM-Pf Complex in Attentional Orienting

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Minamimoto, Takafumi and Minoru Kimura. Participation of the thalamic CM-Pf complex in attentional orienting. *J Neurophysiol* 87: 3090–3101, 2002; 10.1152/jn.00564.2001. The centre médian-parafascicular (CM-Pf) complex is located at the posterior intralaminar nuclei of the thalamus and forms part of the nonspecific thalamocortical projection system and the internal circuit of the basal ganglia. However, the functional roles of this complex remain to be fully elucidated. Here we have examined whether the CM-Pf complex is involved in the process of covert attention. We trained two macaque monkeys to perform a task in which a visual target stimulus for button release appeared at either the same location as the preceding visual instruction cue (a "validly cued target") or a location on the opposite side (an "invalidly cued target"). Reaction times (RTs) to a validly cued target were significantly shorter than those to an invalidly cued target, leading to a "validity effect" of about 20 ms. We recorded the activity of 97 neurons in the CM-Pf while the monkeys performed the attention task with the hand that was contralateral to the neuronal recording. Seventy CM-Pf neurons showed task-related activity after the appearance of either the instruction cue or the target stimulus: 33 neurons responded with a prominent short-latency facilitation (SLF), whereas 37 responded with a short-latency suppression followed by a long-latency facilitation (LLF). Most of the SLF neurons responded preferentially to a cue appearing on the contralateral side (76%) and to an invalidly cued target appearing on the contralateral side (61%). In contrast, LLF neurons showed a short-latency suppression after the cue stimulus, regardless of whether the cue appeared on the contra- or ipsilateral side (84%). Inactivating the CM-Pf complex by local injection (1 μl) of the $GABA_A$ receptor agonist muscimol (1–5 μg/μl) resulted in a significant increase in the RT to a validly cued target presented on the contra- but not the ipsilateral side. In contrast, inactivating the CM-Pf complex did not affect RTs to invalidly cued targets on either the contra- or the ipsilateral side. Thus the validity effect was abolished only on the contralateral side. We conclude that the CM-Pf complex plays a specific and essential role in the process of attentional orienting to external events occurring on the contralateral side, probably through the projection of primary outputs to the striatum, which is involved in the action-selection mechanisms of the basal ganglia.

INTRODUCTION

The intralaminar thalamic nuclei (ILN) were originally thought to be a major part of the so-called "nonspecific" thalamocortical system after the pioneering physiological studies of Dempsey and Morison (1942). Subsequently, the ILN were found to comprise part of a nonspecific reticular activating system that relays the activity of reticular formation to extensive cortical areas (see Groenewegen and Brendse 1994). More recently, however, distinct sets of inputs to the ILN and projections from the ILN to restricted areas of cerebral cortex and the basal ganglia have been identified. The inputs come from the thalamic reticular nucleus (TRN) (Royce et al. 1991; Steriade et al. 1984), the brain stem cholinergic system (Erro et al. 1999; Paré et al. 1988; Parent et al. 1988), the superior colliculus (Grunwerg and Krauthamer 1992; Ichinohe and Shoumura 1998; Krout et al. 2001), the internal segment of the globus pallidus (Sidibé et al. 1997), and the substantia nigra pars reticulata (de las Heras et al. 1998), as well as from the midbrain reticular formation (Royce et al. 1991; Vertes and Martin 1988).

Although these characteristic inputs make the ILN functionally distinct from specific sensory relay nuclei in the thalamus, very few experiments have examined the functional roles of the ILN. Contralateral visual neglect was reported to occur after lesions of the ILN in the cat (Orem et al. 1973) and in humans (Watson and Heilman 1979). Schlag and Schlag-Ray (1984) found that many neurons in the primate rostral ILN (centralis lateralis and paracentralis) have visuomotor response properties in eye-movement tasks. Unlike neurons located in eye-movement centers, such as the superior colliculus and frontal eye field, ILN neurons have a large visual receptive field, are insensitive to stimulus size, shape or brightness, and fire with changes in the visual scene. Thus it was thought that the ILN might be involved in elaborating control (i.e., starting or stopping) signals for eye movement rather than in generating the eye-movement signal per se. More recently, a functional imaging study has indicated that human reticular formation and the centre médian and centralis lateralis of the ILN are activated specifically when an attention-demanding task is performed (Kinomura et al. 1996). It was therefore suggested that reticular formation and the ILN are involved specifically in attentional processes.

The TRN is known to modulate strongly the activity of both specific relay nuclei and the ILN in the thalamus through its GABA-mediated inhibitory actions (Jones 1997). Several studies of the TRN have indicated that the TRN may be involved in the process of attention (McAlonan et al. 2000; Steriade et al. 1986; Weese et al. 1999; Yingling and Skinner 1976).

Recently, single-neuron activity was recorded in the centre

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médian-parafascicular (CM-Pf) complex—the posterior group of the ILN—of monkeys performing behavioral tasks, and CM-Pf neurons were found to encode information about the onset of behaviorally significant multimodal stimuli (Matsumoto et al. 2001). Notably, inactivating the CM-Pf complex by local infusion of muscimol abolished the responses of striatal neurons to sensory stimuli; this indicated that the ILN supplies the striatum with information about behaviorally significant external events with orienting value. Thus the characteristic neuronal activity in the CM-Pf complex might be generated, in part, by the strong influence of inputs from the TRN and from the midbrain reticular formation.

Although the CM and Pf project to neocortex, their main outputs are directed to restricted areas of the striatum: that is, the CM projects to the putamen and the Pf projects to the caudate nucleus (Sadikot et al. 1992a,b; Steriade et al. 1997). The CM-Pf complex is thus positioned to control functions of the basal ganglia effectively. Although neurons in the CM-Pf complex have been observed to respond to behaviorally significant multimodal stimuli (Matsumoto et al. 2001), this does not demonstrate unequivocally that these neurons have an attentional rather than a sensory role. In this study, we aimed to determine specifically whether, and if so how, the CM-Pf complex is involved in attentional mechanisms. To measure covert attentional processes, we have used a cued-reaction time task, originally devised by Posner (1980), in which a cue that precedes a target in the same location decreases the reaction time (RT) to the target, compared with a cue that misdirects attention to a different location. We recorded the activity of single neurons in the CM-Pf complex of monkeys while they performed the task. By examining the effects of inactivating the CM-Pf on the animal's task performance, we have tried to identify the role of the CM-Pf complex in covert orienting.

Here we present findings that suggest that most of the CM and Pf neurons respond to a visual cue that draws the subject's attention to the contralateral side. We also show that neuronal activity in the CM-Pf complex is necessary to decrease the RT to a visual target stimulus appearing at the same location as the cue stimulus. We propose that one of the main functions of the posterior ILN (CM-Pf complex) is to encode information for attentional processing and that this is achieved primarily through the transmission of CM-Pf outputs to the striatum, which in turn is involved in the action-selection mechanisms of the basal ganglia.

METHODS

Behavioral paradigms

Two male macaque monkeys (*Macaca fuscata*: *monkey SS*, 7.8 kg, and *monkey IN*, 6.6 kg) were used in this study. All surgical and experimental procedures were approved by the Animal Care and Use Committee of Kyoto Prefectural University of Medicine. Monkeys were trained to sit in a primate chair facing a small panel 24 cm in front of them. A small light-emitting diode (LED, 0.7° diam and 48 cd/m^2) and two large LEDs (3.3 × 3.3° and 75 cd/m^2) were attached to the panel. The small LED located at the center served as a fixation spot, while the two large LEDs located to the right and left of the fixation spot at a distance of 20° from the fixation spot served as cue and target light. A push button located at the bottom of the panel served as a hold button. When the hold button was illuminated, the monkeys were required to press the button to start the behavioral tasks. The fixation LED was illuminated while the monkeys pressed the hold button. The monkeys oriented their gaze to the illuminated fixation LED and maintained fixation throughout the trial. At random time intervals after the fixation (0.5–1.5 s), one of the two large LEDs was illuminated in red for 83 ms; this served as a cue to attract the animal's attention. At 100, 400, or 700 ms after the cue onset, one of the two large LEDs was illuminated in green, which served as a target. Figure 1*B* depicts the time order of the task. The monkeys were required to release the hold button as quickly as possible and received a drop of reward water if they released the button within 500 ms after the target appeared. An RT of less than 100 ms was considered anticipatory, and the trial was aborted. If the monkeys failed to fixate eyes within a 3° window, the trial was also aborted. The intertrial interval was varied randomly between 3 and 5 s. Both monkeys were trained to perform this task with either arm.

There were two cue conditions in this task (see Fig. 1*A*). In the "valid cue condition," the target appeared at the same location as the cue (80% of trials). In the "invalid cue condition," the target appeared at the opposite side of the cue (20% of trials). The difference in RT between the valid and invalid cue condition, "the validity effect," was used as a measure of the effects of directed attention on target detection and on reaction to it.

Each session comprised about 100–180 trials, and the monkeys performed 5–10 sessions per day. An equal number of right- and left-handed trials were assessed. The two monkeys had been fully trained for 3 mo before behavioral data were obtained.

Surgery

Before the behavioral training, four head-restraining bolts and one stainless-steel recording chamber were implanted with stereotaxic guidance into the skull of each monkey. Before surgery, monkeys were anesthetized with ketamine hydrochloride (6 mg/kg im) and pentobarbital sodium (Nembutal, 27.5 mg/kg ip), and supplemental

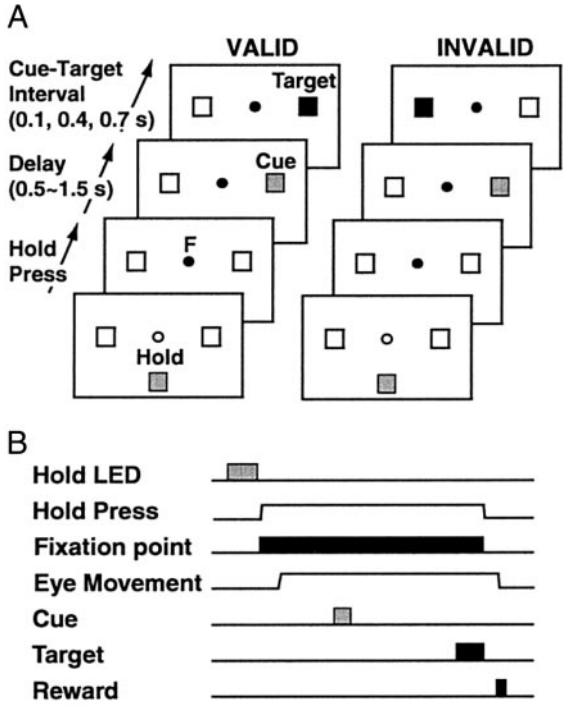

FIG. 1. Experimental paradigm. *A*: illustration of the valid cue condition, in which the cue and the target appear at the same location, and the invalid cue condition, in which the cue and the target appear at different locations. Time progresses from *bottom left* to *top right* as indicated by the arrows on the left. *B*: time order of events in the 2 conditions. Targets are presented at varying intervals after the cue.

Nembutal (10 mg/kg/2 h im) was given as needed. A chamber was positioned vertically for recording neuron activity in the thalamus bilaterally. The center of the chamber was adjusted according to Horseley-Clark stereotaxic coordinates (lateral 0 mm and anterior 11 mm for both monkeys).

Recordings

Single-neuron activity was recorded extracellularly from the CM-Pf complex of four hemispheres using epoxy-coated tungsten microelectrodes (FHC, 26–10^{-2} L) with an exposed tip of 25 μm and an impedance of 2–5 MΩ. The electrodes were inserted through the implanted recording chamber and advanced by means of an oil-drive micromanipulator (Narishige, MO-95). Neuronal activity recorded by the microelectrodes was amplified and displayed on an oscilloscope by using conventional electrophysiological techniques. Band-pass filters (50-Hz to 3-kHz band-pass with a 6-dB/octave rolloff) were used. The action potentials of single neurons were isolated by using a spike sorter with a template-matching algorithm (Alpha Omega, MSD4), and the onset times of the action potentials were recorded on a laboratory computer (NEC9821Bf) together with onset and offset times of stimulus and behavioral events occurring during behavioral tasks.

We studied the activity of CM-Pf neurons while the monkeys performed the tasks with their contralateral hand, although the monkeys occasionally performed the task with their ipsilateral hand. Electromyographic (EMG) activity was recorded from the triceps and biceps brachii muscles (prime movers of the arm) as well as from other supporting muscles through chronically implanted, multistranded Teflon-coated stainless-steel wire electrodes (Cooner Wire AS631) with leads that led subcutaneously to the head implant. The EMG signals were amplified, rectified, integrated, and monitored on-line on a computer display along with the recorded neuronal activity.

Eye movements were also monitored by measuring the corneal reflection of an infrared light beam through a video camera at a sampling rate of 250 Hz. The computer system (RMS R-21C-A) determined horizontal and vertical signals of the center of the reflected infrared light beam. The spatial resolution of this system was ca. $\pm$0.15°. The muscle activity and eye position signal from the video system were also fed to the laboratory computer through the A-D converter interface at a sampling rate of 100 Hz.

Injection of muscimol into the CM-Pf complex in the thalamus

To inactivate neuronal activity in the CM-Pf complex, we injected the $GABA_A$ receptor agonist muscimol (Sigma) locally into the CM-Pf complex of *monkey SS.* The injection protocols were essentially the same as those described previously (Matsumoto et al. 2001) except that here we injected a volume of 1 μl containing 1 or 5 μg muscimol/1 μl saline, pH 7.3. The monkey performed the task with the hand that was contralateral to the muscimol injection.

Data analysis

Behavioral data were obtained and pooled into a single database during the whole recording period. In each muscimol injection experiment, behavioral data were accumulated and pooled into two data sets corresponding to before or after injection. In the behavioral task, two factors could influence the RT to the targets: the cue-target interval (100, 400, or 700 ms) and the cue condition (valid or invalid). We therefore performed a two-way ANOVA to determine the relationship of the RT to the cue-target interval and the cue condition. From the ANOVA results, the significance of the validity effect was evaluated. To analyze the effects of muscimol injection on the RT, we also used a two-way ANOVA using the factors cue-target interval and injection condition (before and after muscimol injection). We report the ANOVA results as F values and significance levels. To compare the difference between two samples (e.g., average percentage of correct performance between 2 conditions), we used Student's unpaired t-test.

The responses of neurons were determined in perievent time histograms of neuronal impulse discharges as an increase or decrease of discharge rate after a behavioral event, relative to discharges during the intertrial interval (500–2000 ms before presentation of the hold LED). The responses were regarded as significant if the change of discharge rate achieved a significance level of $P < 0.05$ by a two-tailed Wilcoxon test (Kimura 1986). We determined the magnitude of task-related discharges within a fixed time window on the basis of the average latency and duration of the whole population of the specific type of neuron. Baseline activity was determined as the average discharge rate during the intertrial interval. Neuronal responses, 2 cue responses (ipsilateral and contralateral), and 12 target responses (combinations of 2 cue conditions, 2 target sides, and 3 cue-target intervals) were compared quantitatively with baseline activity by using ANOVA and post hoc Bonferroni test in most cases.

Histological reconstruction

At the end of all of the recording experiments, small electrolytic lesions were made at several locations along selected electrode tracks in the CM-Pf complex. A direct anodal current (20 μA) was passed for 30 s through tungsten microelectrodes. Each monkey was anesthetized deeply with Nembutal (60 mg/kg ip) and then perfused transcardially with 4% paraformaldehyde in 0.1 M phosphate buffer. Coronal sections (50-μm thick) through the CM-Pf complex of both hemispheres were stained with cresyl violet or by the thiocholine method to highlight acetylcholinesterase (AChE) activity (Graybiel and Berson 1980; Hardy et al. 1976). Both recording and injection electrode trucks were reconstructed in reference to the lesion marks. The recording sites of neurons and injection sites were estimated along each truck and are expressed in approximate Horsley-Clark coordinates (Kusama and Mabuchi 1970) as shown in Fig. 8.

RESULTS

Behavioral results of attention task

After 3 mo of training, both monkeys performed the task with a high percentage of correct performance (average 89.7% for *monkey SS*, 93.4% for *monkey IN*). During the experimental period (about 2 mo), monkeys performed more than 20,000 trials. Both monkeys responded to targets presented at the same location as the cue (validly cued target) with significantly a shorter RT than to targets presented on the opposite side (invalidly cued target). For *monkey SS*, the mean $\pm$ SD of the RTs across all cue-target intervals was 240 $\pm$ 53 and 254 $\pm$ 67 ms for the valid and invalid conditions, respectively. The mean, 14.0-ms difference or "validity effect" was highly significant [main effect of cue condition, $F(1,24774) = 250.6$, $P \ll 0.001$]. The validity effect was largest (26.6 ms) at a cue-target interval of 400 ms [interaction of cue condition and cue-target interval, $F(2,24774) = 60.8$, $P < 0.001$]. For *monkey IN*, the RTs decreased as a function of cue-target interval [main effect of cue-target interval, $F(2,45041) = 1414.6$, $P < 0.001$]. The validity effect was smaller than for *monkey SS* (valid RT, 244 $\pm$ 52 ms; invalid RT, 256 $\pm$ 63 ms; validity effect, 10.9 ms) but still significant [$F(1,45041) = 132.7$, $P < 0.001$] and was largest (13.5 ms) at a cue-target interval of 400 ms [interaction of cue condition and cue-target interval, $F(2,45041) = 26.9$, $P < 0.001$]. Figure 2, *A* and *B*, illustrates the average RTs of *monkeys SS* and *IN*, respectively, at three

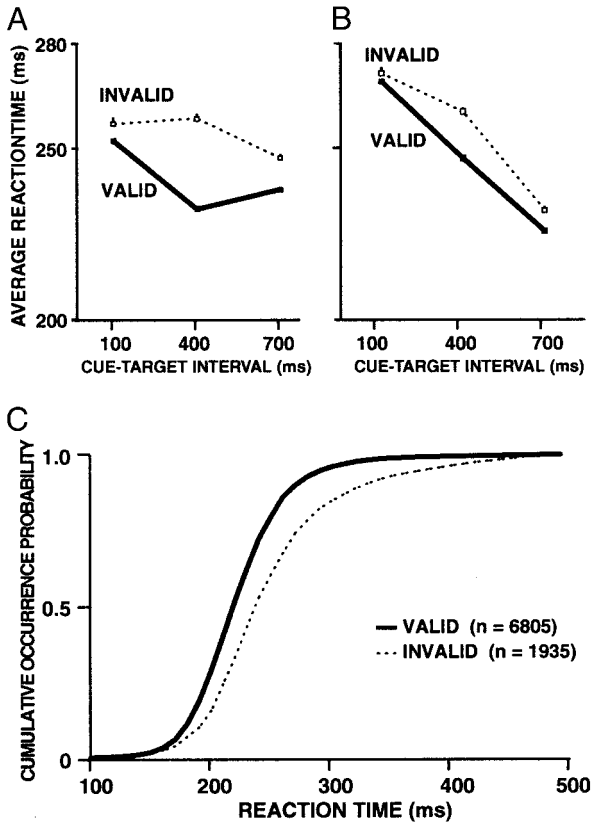

FIG. 2. Comparison of average reaction times (RTs) in both valid and invalid cue conditions along with cue-target interval in *monkey SS* (*A*) and *monkey IN* (*B*). Note that RTs in the valid cue condition (—) are clearly shorter than those in the invalid cue condition (· · ·) at the middle cue-target interval (400 ms). *C*: cumulative occurrence probability of RTs in both conditions at the middle cue-target interval. Data were collected for 2 mo after the training period. Error bars indicating SE are plotted, but most of them are smaller than the actual data points.

different cue-target intervals. At an interval of 400 ms, the cumulative distribution of RTs showed that the response was faster to the validly cued target than to the invalidly cued target for *monkey SS* (Fig. 2*C*), as indicated by the relative shift of the valid condition curve (—) to the left. The smaller validity effect at short (100 ms) and long (700 ms) cue-target intervals, compared with the middle cue-target interval, suggests that the animals' attention remains at the position where the cue was presented less frequently at these intervals than at the middle interval.

We recorded the activity of four prime mover muscles of both arms during task performance. Representative activity of the biceps brachii muscle during both the valid and the invalid conditions is shown in Fig. 3*A*. The average traces of the muscle activity in the valid (solid line) and the invalid (thin line) conditions indicate that the patterns of muscle activation in the two conditions were very similar, being composed of initial and later components (Fig. 3*B*). The traces also show that the biceps brachii muscle was activated earlier in the valid than in the invalid conditions; this would give rise to the shorter RTs observed in valid conditions.

Activity of CM-Pf neurons

We recorded the activity of 97 neurons in the CM-Pf complex in four hemispheres of the two monkeys. Seventy of these neurons

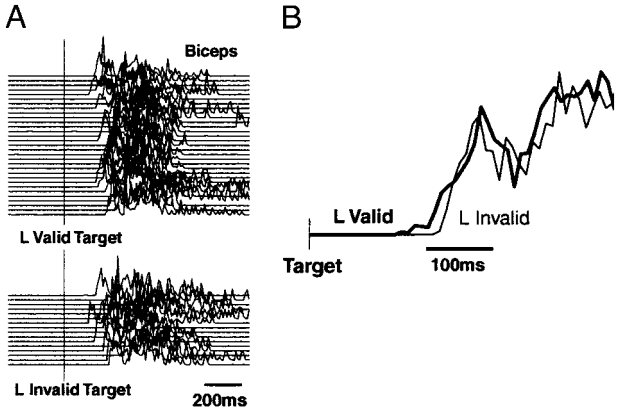

FIG. 3. Prime muscle activity in the valid and invalid cue conditions in *monkey SS*. *A*: representative example of electromyographic (EMG) patterns of the right biceps brachii muscle. *B*: comparison of average EMG curves of the valid (thick line) and the invalid (thin line) conditions. Note that onset of EMG activity was earlier by about 30 ms in the valid condition.

exhibited significant visual responses at a short latency to the external events (hold-, cue-, and target-LED) that appeared in the task. Neurons were classified according to the latency of activation after the appearance of visual stimuli as described previously (Matsumoto et al. 2001). Thirty-three neurons responded to the cue and/or target stimuli during the task with burst discharges at short latency (58 ± 22 ms), corresponding to the short-latency facilitation (SLF) type of neurons described by Matsumoto et al. (2001). The other 37 neurons showed suppression of their background discharges at short latency (98 ± 29 ms) after the cue and/or target stimuli, followed by facilitation at long latency (278 ± 39 ms), corresponding to the long-latency facilitation (LLF) type of neurons described by Matsumoto et al. (2001). The long-latency facilitation of the LLF neurons occurs too late to be involved significantly in the neuronal mechanisms responsible for the validity effect. Therefore we focused our studies on the facilitatory responses of the SLF neurons and on the short-latency suppressive responses of the LLF neurons.

Short-latency responses of CM-Pf neurons to cue and target

Both cue and target visual stimuli elicited significant responses in many SLF neurons, especially when the stimuli appeared on the contralateral side of the neuronal recording (Table 1). An example of the activity recorded from an SLF neuron in the Pf is shown in Fig. 4. This neuron responded with

TABLE 1. *Visual responses of CM-Pf neurons in attention task*

	SLF	LLF
Cue		
Ipsilateral	15 (45)	31 (84)
Contralateral	25 (76)	31 (84)
Target		
Ipsilateral valid	6 (18)	23 (62)
Contralateral valid	13 (39)	25 (68)
Ipsilateral invalid	13 (39)	27 (73)
Contralateral invalid	20 (61)	30 (81)
Total	33 (100)	37 (100)

Number of short- and long-latency facilitation (SLF and LLF) neurons responding to different cue and target conditions and corresponding percentage (in parentheses). Note that only short-latency suppressive responses were counted in LLF neurons. CM-Pf, centre médian-parafascicular.

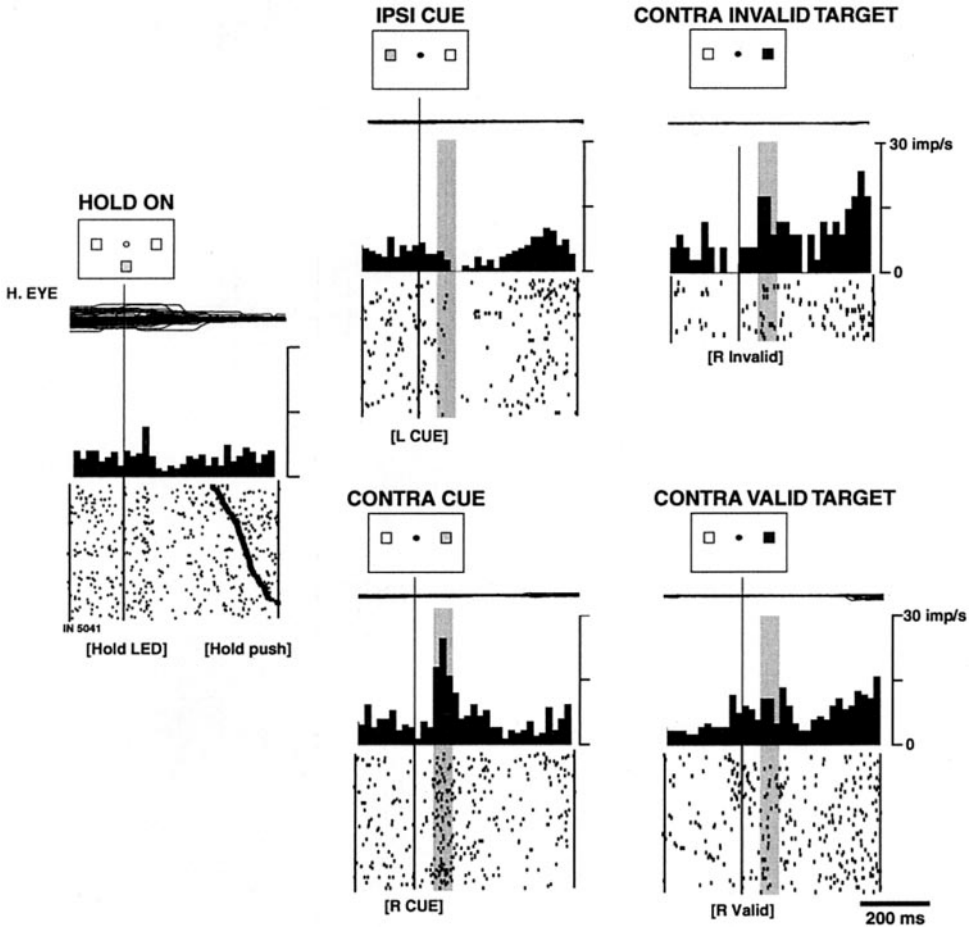

FIG. 4. Representative activity of a parafascicular (Pf) neuron that showed short-latency facilitatory responses to visual cues in the task. The rasters and histograms of spike discharges are aligned at the onset time of the hold, cue or target light-emitting diode (LED). Histograms indicate superimposed traces of horizontal eye position signal. ▨ the time window (60–120 ms) for measuring the cue or target response.

a short-latency activation when a cue and invalid target appeared on the contralateral side but did not respond when either a cue appeared on the ipsilateral side or a valid target appeared on the contralateral side.

Population analysis also indicated that SLF neurons responded to cue stimuli appearing on the contralateral side, but not on the ipsilateral side (Fig. 5*A*). However, responses to target stimuli appearing on the contralateral side depended highly on the cue condition. Figure 5*B* shows that although SLF neurons were activated when invalidly cued targets were presented on the contralateral side, they responded less intensely to validly cued targets presented on the contralateral side. The population activity histograms in Fig. 5 include neurons recorded in both *monkeys SS* and *IN* because the two groups of neurons behaved similarly in both monkeys. Together, these observations indicate that the neuronal responses are enhanced when the animals' attention shifts to the contralateral hemifield.

In contrast, LLF neurons showed a short-latency suppression after cue and/or target stimuli regardless of the laterality (Table 1). An example of the activity recorded from this type of neuron is shown in Fig. 6. After presentation of the cue, discharges from this neuron were suppressed at a latency of about 80 ms. This suppression was induced by a cue presented on either the ipsilateral or the contralateral side to the neural recording. No significant suppression was recorded after target stimuli in this neuron. Many LLF neurons showed a robust decrease and a subsequent increase in activity after the hold LED was illuminated. As shown in Fig. 6, monkeys made saccadic eye movements to the fixation spot on illumination of the hold LED and the fixation spot LED. Thus the robust decrease and subsequent increase in activity after illumination of the hold LED could contain both sensory responses to the LED and saccade-related activity, and these cannot be distinguished in the spike discharges. By contrast, the cue LED was presented while the monkeys were fixating on the central LED, which excluded the possibility of saccade-related activity. Therefore we could not study the neuronal responses to the hold LED quantitatively. The neuron shown in Fig. 6 also showed LLF after a validly cued target presented on the contralateral side. This facilitation was coincident with release of the hold button, and we will describe this movement-related activity of CM-Pf neurons elsewhere.

To determine the stimuli that elicited the strongest responses, we compared quantitatively the mean neural discharges that occurred under different stimulus conditions. Figure 7*A* shows the mean response magnitudes of the short-latency facilitation of SLF neurons for both monkeys. Compared with the baseline activity, significant SLF responses were evoked when the cue appeared on the contralateral side ($P < 0.05$, post hoc Bonferroni test). In addition, the responses to a contralateral target were largest for the invalidly cued target at a cue-target interval of 400 ms ($P < 0.001$, post hoc Bonferroni test).

To evaluate the attentional effect on the SLF neuronal responses, for each neuron, the magnitude of the response to a

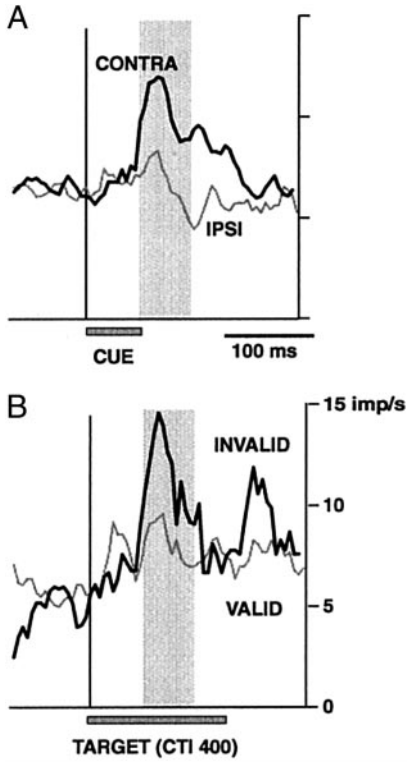

FIG. 5. Average cue and target response curves of short-latency facilitation (SLF)-type neurons. *A*: mean response to a cue appearing on the contralateral hemifield (thick line) as compared with the ipsilateral hemifield (thin line). *B*: mean response to a contralateral validly cued target (thin line) as compared with a contralateral invalidly cued target (thick line). Data are from trials using only the middle cue-target interval (400 ms). The activity across the trials was averaged every 5 ms in 15-ms bins. Shaded bars indicate the time window (60–120 ms) for measuring the cue or target response.

contralateral valid target was subtracted from that to a contralateral invalid target at the three different cue-target intervals for both monkeys. A two-way ANOVA revealed that the differences between the two target responses (i.e., neural validity effects) were largest at a cue-target interval of 400 ms [$F(2,93) = 3.4$, $P < 0.05$, post hoc Bonferroni test] but were not different between the two monkeys [$F(1,93) = 0.0003$, $P = 0.99$]. Therefore the behavioral reactions of each animal during this attention task were reflected well in the response of the SLF neurons to the target.

Quantitative analyses of the short-latency suppression of LLF neurons (Fig. 7*B*) indicated that the visual instruction cue significantly suppressed neuronal activity. A significant suppression of activity occurred with both contralateral ($P < 0.001$, post hoc Bonferroni test) and ipsilateral ($P < 0.001$, post hoc Bonferroni test) cues. In contrast, neither a contralateral nor an ipsilateral target LED evoked significant suppression of discharges. A three-way ANOVA also revealed that cue condition [$F(1,423) = 0.2$, $P = 0.68$], target side [$F(1,423) = 3.1$, $P = 0.08$], and cue-target interval [$F(2,423) = 0.3$, $P = 0.72$] had no significant effect on the neuronal response to the target. Thus in LLF neurons, there is no consistent relationship between target response and cue condition or between target response and the laterality of stimulus presentation.

In summary, stimuli that attract attentional orienting (i.e., the cue itself or an invalidly cued target) to the contralateral side selectively activate SLF neurons. In contrast, cue stimuli, but not target stimuli, suppress the activity of LLF neurons in a manner that is independent of laterality.

Location of task-related neurons

As reported previously (Matsumoto et al. 2001), there was a clear difference in the distribution of the SLF neurons and the LLF neurons that showed short-latency suppression in the CM-Pf complex (Fig. 8). Although some SLF neurons were recorded in the caudal CM, SLF neurons were located predominantly in the Pf and in the transitional zone between the CM and Pf that is composed of medium-sized dark cells of the Pf and smaller and paler cells of the CM (Sadikot et al. 1992a). In contrast, LLF neurons tended to be located exclusively in the CM.

Effects of inactivating the CM-Pf complex on task performance

To determine whether neurons in the CM-Pf complex are important in performing covert orienting tasks, we studied quantitatively the animals' performance in the attention task before and after blocking neural activity in the CM-Pf complex through a local infusion of the $GABA_A$ receptor agonist muscimol. In 10 experiments, we injected 1 μl muscimol (1–5 μg/μl in saline, pH 7.3) into the CM-Pf complex of *monkey SS.* The injection sites of muscimol are shown in Fig. 8. In each experiment, the monkey performed between one and three sessions of trials before the muscimol was injected. We confirmed that the tip of the injection cannula was in the CM or Pf by recording neuronal activity through a Teflon-coated tungsten wire electrode protruding from the tip of the cannula (Matsumoto et al. 2001). *Monkey SS* then performed 5–10 more sessions for ≤3 h after muscimol injection.

The average percentage of correct performance was 88.0% before injection (from a total 15 blocks of 100–180 trials). The main types of error were release of the hold button or breaking of fixation before appearance of the target and release of the hold button too late. After injection of muscimol, *monkey SS* continued to perform the task with a high rate of precision (87.6% in a total of 46 blocks). Thus the rate of correct performance was not influenced (*t*-test, $P = 0.73$) by inactivation of the CM and the Pf .

The effect of muscimol injection on the mean RT in each cue condition is shown in Fig. 9. Before injection, the RT in both the ipsi- and contralateral valid cue conditions was significantly shorter than in the invalid conditions as shown in Fig. 9*A* [contralateral, $F(1,735) = 6.4$, $P < 0.05$; ipsilateral, $F(1,742) = 26.6$, $P < 0.001$]. After muscimol injection, the RT to a contralateral validly cued target became significantly longer than before injection, as shown in Fig. 9*B* [$F(1,1850) = 18.6$, $P < 0.001$]; however, the RT to a contralateral invalidly cued target was not affected significantly [$F(1,544) = 0.2$, $P = 0.63$]. Muscimol also affected the influence of cue-target interval on the RT to a contralateral validly cued target [significant interaction between injection condition and cue-target interval, $F(2,1850) = 6.1$, $P < 0.01$], but not to an invalidly cued target [$F(2,544) = 1.6$, $P = 0.20$]. Thus the difference between the RT to the valid condition and that to the invalid condition—that is, the validity effect—became nonsignificant for contralateral targets after injection of muscimol

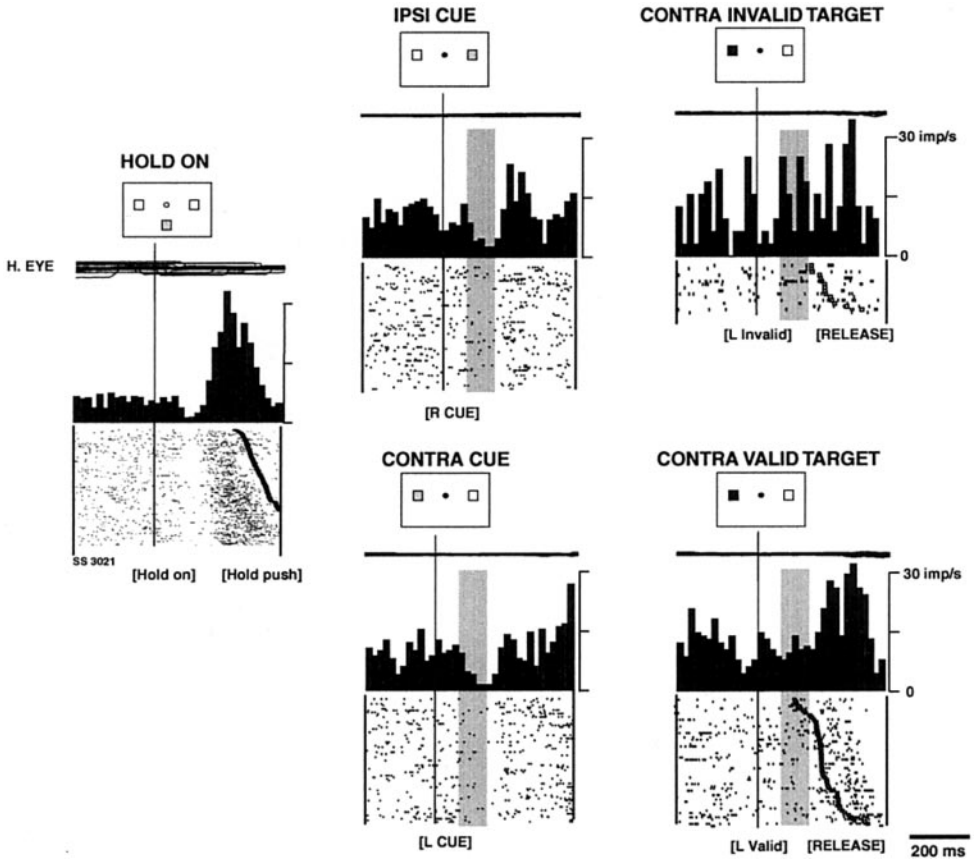

FIG. 6. Representative activity of a centre médian (CM) neuron that showed short-latency suppressive responses to visual cues in the task. Details are given in Fig. 4. ▨, the time window (80–180 ms) for measuring the cue or target response.

[$F(1,1659) = 1.1$, $P = 0.30$]. In contrast, the RT to validly cued ipsilateral targets shortened significantly, and the validity effect remained highly significant [$F(1,1774) = 96.0$, $P < 0.001$]. We thus conclude that inactivation of the CM-Pf complex by muscimol injection results in a loss of the validity effect that is specific to target stimulus presentation on the contralateral side.

To verify that the effects of muscimol injection into the CM-Pf complex were not the result of mechanical damage to the neurons and passing fibers in the CM-Pf, we injected the same or a larger volume of physiological saline (1–3 μl) into the same area of the CM-Pf complex in four experiments (see Fig. 8). After saline injection, the mean RTs to a validly cued target appearing on both the ipsi- and the contralateral sides were still significantly shorter than those to an invalidly cued target, as shown in Fig. 9*C* [ipsilateral, $F(1,1019) = 19.4$, $P < 0.001$; contralateral, $F(1,1016) = 4.5$, $P < 0.05$]. Thus as saline injection had no effect on attentional orienting, the effects observed after muscimol injection must be caused by inhibition of neuronal activity in the CM-Pf.

We next examined the effect of injecting muscimol specifically into the CM or the Pf by measuring the decrease in validity effect over time (Fig. 10). In both cases, the validity effect was significant before muscimol injection. When muscimol was injected into the Pf and the CM-Pf border (5 cases, green circles in Fig. 8), the validity effect was reduced rapidly and became nonsignificant by 30 min. In contrast, when muscimol was injected into the lateral part of the CM (5 cases, brown circles in Fig. 8), the validity effect remained significant at 60 min, after which it reduced gradually to almost zero at 120 min. These different time courses indicate that inactivation of the Pf has a stronger effect on the performance of our attention-shift task than has inactivation of the CM; in addition, the long latency of the effects after muscimol injection into the CM might be caused by diffusion of muscimol into the Pf from the injection sites in the CM.

In a few muscimol injection experiments, we observed effects on the monkey's eye position and posture. In two of five injections into the CM and in two of five injections into the Pf, the monkey stopped performing the task 2–3 h after the injection. In these cases, the slow phases of nystagmic eye movements occurred toward the side that was ipsilateral to the muscimol injection, and when the monkey was returned to its home cage, it tended to make ipsiversive circling movements at a rate of about twice every minute for 2–3 h. However, there was no obvious effect on the pattern of muscle activation during task performance. Activities of biceps brachii muscle before and after muscimol injection are shown in Fig. 11, *A* and *B*, respectively. Before and after injection, initial strong phasic activations were followed first by suppression and then by a small sustained activation (Fig. 11, *A*-*C*). Although the duration of the initial activation did not change significantly, the onset of the initial activation after muscimol injection was delayed by about 40 ms at peak activation (Fig. 11*D*).

DISCUSSION

In this study, we have recorded the activity of neurons in the CM-Pf complex of monkeys performing an attention task. Many neurons showed responses to the hold, cue and target

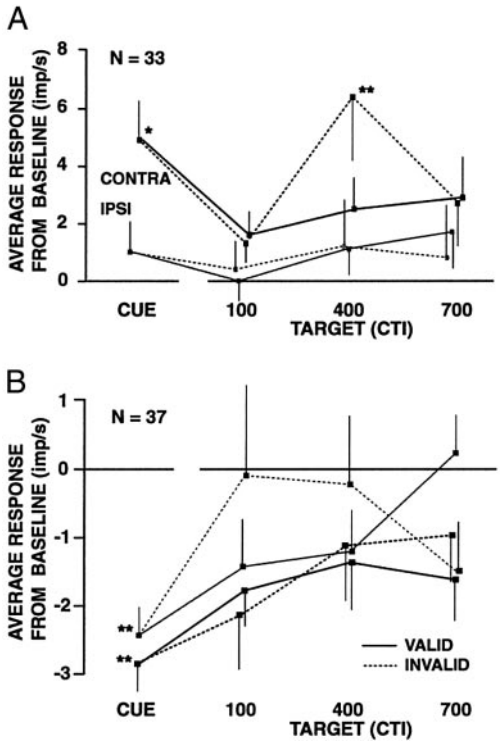

FIG. 7. Comparison of the magnitude of mean neuronal responses to the cue and the target. *A*: SLF responses of SLF-type neurons. *B*: short-latency suppressive responses of long-latency facilitation (LLF)-type neurons. Neuronal discharge rates during the time windows indicated in Figs. 4 and 6 were measured, and the baseline activity was subtracted. Error bars represent SE. ANOVA results: cue responses in *A*, $F(2,96) = 5.4$, $P < 0.01$; target responses in *A*, $F(12,400) = 1.9$, $P < 0.05$; cue responses in *B*, $F(2,108) = 13.5$, $P < 0.001$; target responses in *B*, $F(12,459) = 0.9$, $P = 0.58$. Asterisks indicate a significant difference from baseline activity: $*P < 0.05$ and $**P < 0.001$ (post hoc Bonferroni test).

LEDs, each of which provided key information to perform the task. This is consistent with previous results that showed that neurons in the primate CM-Pf complex respond to multisensory stimuli with behavioral significance (Matsumoto et al. 2001). In addition, the most prominent activity of CM-Pf neurons, in particular SLF neurons, was the response to the cue and to an invalidly cued target, both of which would evoke attentional orienting in the animal. When the CM-Pf complex was inactivated by a local infusion of muscimol, the RT to a validly cued target that appeared on the contralateral side of the inactivation was selectively prolonged, and the validity effect—which is a measure of the effects of directed attention on target detection—disappeared almost completely. These results lead us conclude that the CM-Pf complex has an essential role in the process of attentional orienting.

CM-Pf complex responses to sensory events with orienting value

In the attention task, the principal responses of SLF neurons were evoked by the cue and by an invalidly cued target. The purpose of the cue is to draw an animal's covert attention so that it can react quickly to the appearance of a target at the same location (Posner et al. 1980). An invalidly cued target should also draw an animal's attention because the animal should have been attending a cue on the opposite side. In contrast to the response of SLF neurons, the short-latency suppression of the discharges of LLF neurons was less selective to the laterality of the stimulus. This suppression occurred predominantly after cue stimuli rather than after target stimuli. This suggests that LLF neurons may also encode information for external stimuli that draw an animal's attention.

Neurons in the superior colliculus (SC) and the parietal cortex of primates, which have been proposed to play a major role in attentional shift, also respond predominantly to the cue and an invalidly cued target in the same attention task that we used here (Robinson and Kertzman 1995; Robinson et al. 1995). The CM-Pf complex receives inputs from many regions of the brain stem, including the deep layer of the SC (Ichinohe and Shoumura 1998; Krout et al. 2001), the pedunculopontine nucleus (PPN) (Erro et al. 1999; Paré et al. 1988; Parent et al. 1988), and the locus coeruleus (LC) (Royce et al. 1991). Neurons in the deep layers of the SC respond to multisensory stimuli and their receptive fields are fairly large and located mainly on the contralateral side (Wallace et al. 1996). During

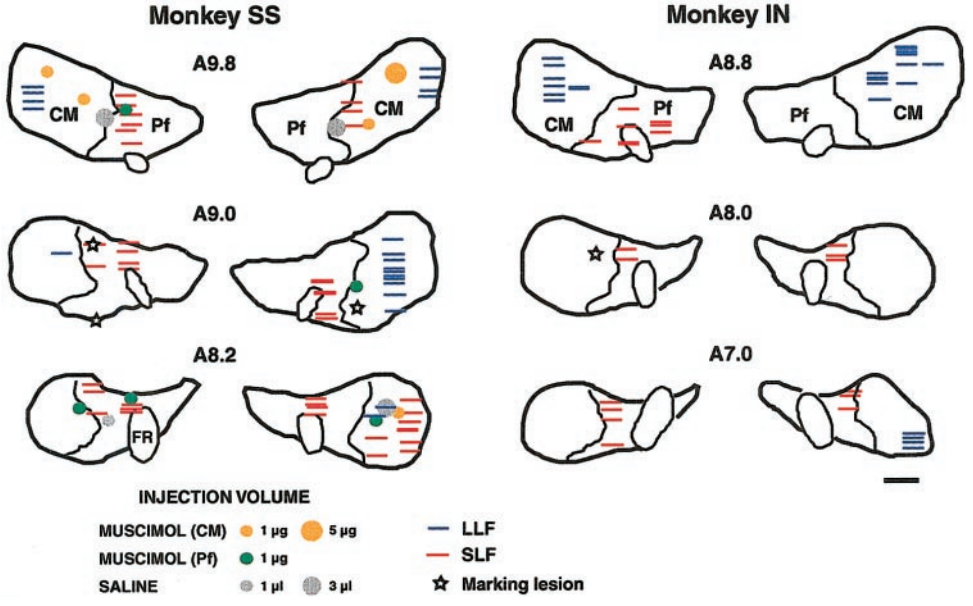

FIG. 8. Locations of SLF- and LLF-type neurons in the CM and Pf of *monkeys SS* and *IN*. Red bars indicate recording sites of SLF responses from SLF-type neurons and blue bars indicate those of short-latency suppression responses from LLF-type neurons. Filled circles indicate the locations and injection volumes of muscimol in the CM (brown) and in the Pf and CM/Pf border (green), and injection sites of saline in the CM-Pf (gray), respectively. FR, fasciculus retroflexus. Scale bar, 1 mm.

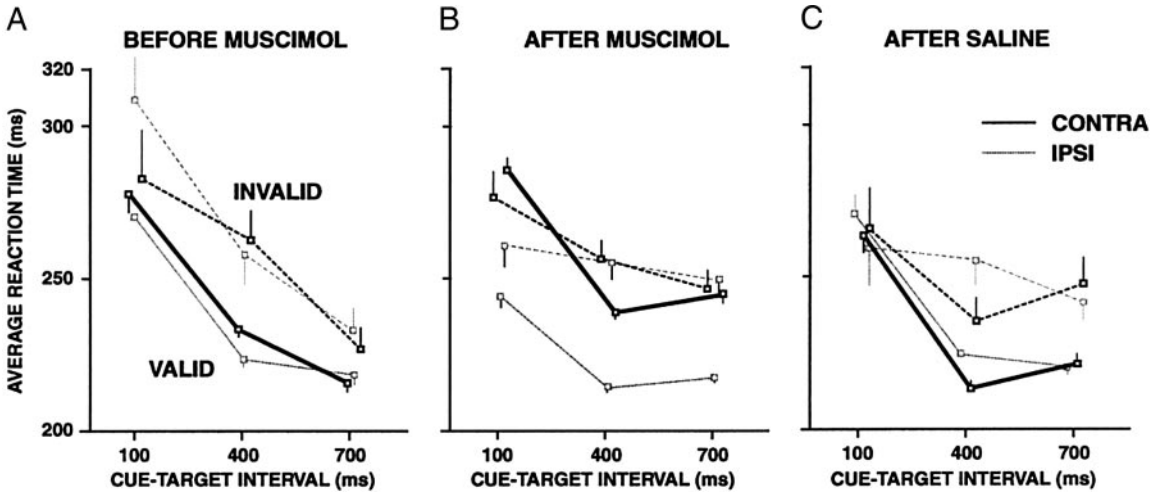

FIG. 9. Effect of inactivating the CM-Pf complex on the mean RT for each cue condition. *A*: before muscimol injection. RTs for valid conditions are faster than for invalid conditions. *B*: after muscimol injection. For responses to contralateral targets, there is no significant difference in the RTs for valid and invalid conditions. *C*: after saline injection (control). Solid and dotted lines indicate valid and invalid conditions, respectively. Black lines indicate contralateral and dark lines indicate ipsilateral target trial, respectively. Bars indicate SE.

a detection task, noradrenergic neurons in the LC are phasically activated at a short latency (about 100 ms) not only by a target stimulus but also by other unexpected sensory stimuli that usually produce an orienting reaction (Aston-Johns et al. 1994). The activity of PPN neurons—some of which have been considered to be cholinergic—may reflect attention and vigilance (Steriade et al. 1990). Thus the variety of projections from these multiple brain stem sources to the CM-Pf are likely to contribute to the sensory responses of CM-Pf neurons that have orienting value.

We found here that the SLF-type neurons were located predominantly in the Pf, whereas the LLF-type neurons were restricted mainly to the CM as reported previously (Matsumoto et al. 2001). It is possible that this spatially different representation of neuronal functions within the CM-Pf complex is related to functional differences in the projection targets of the two structures, such as the predominant innervation of Pf on the caudate nucleus and that of CM on the putamen (Sadikot et al. 1992a,b; Steriade et al. 1997). But to date there has been no anatomical evidence to indicate the differential afferent innervation of the CM and the Pf (Jones 1997), and so the origins of the differential localizations of SLF and LLF neurons are currently unclear. We suppose that local circuits in the CM-Pf complex and/or the surrounding nuclei, including the thalamic reticular nucleus (TRN), may be responsible for the differential properties of SLF and LLF neurons. In fact, after sensory stimuli, LLF neurons show a significant suppression of their discharges at a short latency that is compatible with the activation of SLF neurons. Unique but unknown projections to the CM and the Pf might be also the source of the differential activity of the SLF and LLF neurons.

With regard to the short-latency suppression of LLF neurons, there are three candidates for the inhibitory input sources:

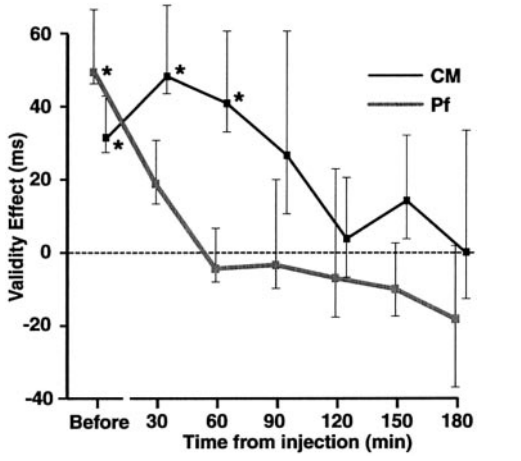

FIG. 10. Differential effects of muscimol injection into the CM or the Pf on the temporal change in validity effect. Average validity effects are plotted as a function of time before and after muscimol injection into the CM (5 cases, dark thin line) or into the Pf and CM/Pf border (5 cases, gray thick line). The average validity effects are plotted from trials in which the target was presented on the contralateral side at a cue-target interval of 400 ms. Asterisk indicates a significant validity effect ($P < 0.05$, *t*-test). Note that error bars are asymmetric, because the SEs of the invalid and valid conditions are plotted respectively as bars above and below each average plot.

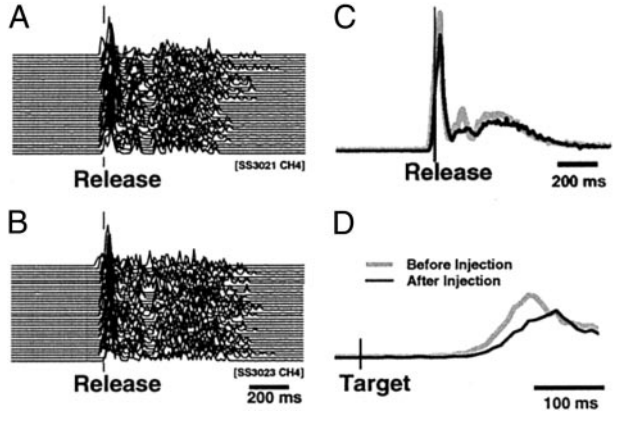

FIG. 11. Prime mover muscle activity during trials in which a validly cued target was presented on the contralateral side in *monkey SS*. *A* and *B*: representative examples of the muscle activity of the left biceps brachii before (*A*) and after (*B*) muscimol injection. *C* and *D*: comparison of the average EMG activity before (thick gray line) and after (thin dark line) muscimol injection during 5 experiments, aligned either at button release (*C*) or at target presentation (*D*).

the internal segment of the globus pallidus (Sidibé et al. 1997), the substantia nigra pars reticulata (de las Heras et al. 1998), and the TRN (Steriade et al. 1984). It has been shown recently that lesion of the TRN abolishes attentional orienting to a visual stimulus that appears on the side that is contralateral to the lesion (Weese et al. 1999) and also that Fos-positive neurons are more numerous in the sector of the TRN that is associated with attended conditioned stimuli than in the sector that is associated with unattended stimuli (McAlonan et al. 2000). Thus the TRN seems to play a crucial role in processing sensory gating and attentional information (Guillery et al. 1998; McAlonan et al. 2000). Inhibitory projections from the internal segment of globus pallidus and the substantia nigra pars reticulata could also have significant influence on the suppression of LLF neurons through which the basal ganglia might contribute to an orienting response.

The neurons in the CM-Pf responded predominantly to a visual cue or a target appearing on the contralateral side (SLF-type neurons) or to a visual stimuli appearing on either the ipsilateral or the contralateral side (LLF-type neurons). These types of neuronal response, which encode information on behaviorally significant external events, are also consistent with those of neurons located in another area of the ILN of the thalamus (Schlag and Schlag-Ray 1984).

Inactivation of the CM-Pf complex abolishes attentional shift

Our results showed that unilateral inactivation of the CM-Pf results specifically in an increase in the RT to a contralateral target preceded by a cue appearing on the same location (valid condition). The RT to a target is faster when attention is directed to the location where the target will appear than when attention is directed to another location (Eriksen and Hoffman 1972; Posner 1988). This is due to the benefit in directing attention to the location where the target will appear or to the cost of misdirecting attention or a combination of both.

After the CM-Pf complex was inactivated by muscimol injection, the RT advantage provided by valid cues presented on the contralateral side was abolished, although the low error rate and the typical activation pattern of the prime mover muscles for task performance remained the same. This indicates that the CM-Pf complex is part of a system that relays the benefits from directing attention. This complex may contribute to focus and facilitate sensorimotor processing on the cued location by transmitting information on the occurrence or cessation of external events with attentional value to the basal ganglia and the cerebral cortices (Steriade et al. 1997). By contrast, muscimol injection did not affect the RT to an invalid target presented on the contralateral side. This suggests that the CM-Pf complex may be involved in modifying sensorimotor processing rather than playing a major role in detecting the target or in generating a behavioral reaction to the target. The CM-Pf complex might either enhance detection of the target or decrease the RT to the target or possibly both. The lack of a significant effect on the RT to an invalidly cued target also indicates that vigilance and arousal level are not affected by inactivation of the CM-Pf complex.

As muscimol injection into the Pf produced quicker effects than injection into the CM, the responses of SLF neurons to a cue stimulus on the contralateral side are likely to encode orienting signals transmitted to focus and facilitate sensorimotor processing at the cued location. One could argue, however, that this explanation is not consistent with the observation that the SLF neurons exhibited a strong response to contralateral *invalid* targets. Although an invalid target would cause an attentional shift, the speed of sensorimotor processing should depend on whether attention had been oriented to the target location before the target actually appeared, as in the valid condition. In other words, the primary behavioral effect of the inactivation of the Pf on the cued-reaction time is probably mediated through blocking the SLF response to a cue stimulus. Thus as mentioned in the preceding text, the CM-Pf complex, and in particular the SLF neuronal activity in the Pf, seems more likely to have a role in modifying sensorimotor processing than in producing a behavioral reaction to the target.

In a few muscimol injection experiments, we observed an effect on the monkey's eye position and posture. It seems unlikely that these effects were produced by inactivation of the CM-Pf because they were not observed in most of the injection experiments, in which changes were observed in attentional shift. Instead, these effects on the eyes and axial musculature may have resulted from diffusion of muscimol into the surrounding thalamic nuclei such as other ILN and the ventral posterolateral (VPL) nucleus, in which it has been shown that lesions induce contralateral visual neglect (Orem et al. 1973), eye-movement-related neurons are localized (Schlag and Schlag-Ray 1984), and electrical stimulation evokes discrete body movements (Vitek et al. 1996). The very long latency of the effects of muscimol injection on eye and body movements (2–3 h) observed here supports the idea of muscimol diffusion into other areas.

Comparison of the CM-Pf with other attention-related brain areas

Although injury to a few areas of the human brain causes a reduction in the ability to shift attention covertly or with eye movement, each area seems to produce a different type of deficit. According to this difference, Posner et al. (1984) proposed that there are three fundamental components of attentional shift—exogenous, bottom-up, and covert orienting—and that these components are associated with different brain regions: the parietal cortex is proposed to disengage attention (Petersen et al. 1989; Posner et al. 1984, 1987); the superior colliculus is proposed to shift attention (Posner and Driver 1992; Robinson and Karzman 1995); and the lateral pulvinar of thalamus is proposed to engage the new location (Petersen et al. 1987; Posner and Driver 1992; Rafal and Posner 1987). It has also been suggested that these three structures, which are known collectively as the "posterior attention network," cooperate in orienting attention to a location in space (Posner 1990).

In contrast, the prefrontal cortex and anterior cingulate cortex, known collectively as the anterior attention network, seem to be important in planning functions in attention, the deficits of which can be visualized effectively by the Wisconsin Card Sorting test and Stroop interference test, rather than in the visuospatial orienting of attention that the posterior attention network is involved in. The anterior attention network presumably plays a top-down role in sifting out behaviorally relevant information from competing information (Casey et al. 2000). Rosen et al. (1999) have suggested that the prefrontal cortex may be involved in voluntary shift of attention (endogenously

attentional orienting) but not in reflexive shift to external stimuli. Much recent evidence indicates that the basal ganglia, although not actually involved in the anterior attention network, have a role in attention mechanisms (Boussaoud and Kermadi 1997; Casey et al. 2000; Coull et al. 2000; Matsumoto et al. 2001; Ravizza and Ivry 2001; Teicher et al. 2000).

Although the CM-Pf complex inputs come from many different brain stem nuclei, the outputs are directed mainly to the action-generating system—that is, the basal ganglia (the striatum and subthalamus) and the frontal cortices (Sadikot et al. 1992a). Thus the CM-Pf complex may act as a key input station for the action-selection function of the basal ganglia by supplying the basal ganglia with information of attentional orienting value.

Functional implications of projections from the CM-Pf to the striatum

In addition to the cerebral cortex, the CM-Pf complex is a major source of glutamatergic afferents to the striatum. Recent anatomical data have indicated that the thalamostriatal projections originating from the CM-Pf complex are massive and topographically organized. Inputs from the CM to the striatum project extensively to the postcommissural sensorimotor part of the putamen, whereas the inputs from the Pf innervate predominantly the limbic-associative striatal territories (Sadikot et al. 1992a,b). Interestingly, in this study we observed movement-related activity exclusively in LLF-type neurons, which were predominantly located in CM. In contrast to cortical terminals, which form mostly axo-spinous synapses, CM and Pf inputs terminate preferentially on the dendritic shafts of both striatal medium-sized spiny neurons (Kemp and Powell 1971; Sadikot et al. 1992b) and cholinergic interneurons (Lapper and Bolam 1992; Sidibé and Smith 1999). Thus both CM and Pf inputs to the striatum must exert strong influences on the principal striato-pallidal and/or striato-nigral information processing streams in the basal ganglia.

In the monkey, the thalamostriate projections that originate from the CM-Pf complex have been shown recently to contribute extensively to the sensory responses of the striate neurons by transmitting information about behaviorally significant sensory events (Matsumoto et al. 2001). Thus the projections from the CM-Pf complex to the striatum might function in selecting action plans on the basis of selective attention.

For example, when an unexpected stimulus is presented, the SLF-type neurons, which are located mainly in the Pf and the caudal part of the CM, should transmit signals about the onset of the stimulus if it occurs on the contralateral side to the striatum. This signal transmission would, at least in part, have a crucial role in orienting attention to a specific spatial location and in shortening the behavioral reaction to it. In support of this, striate projection neurons and tonically active interneurons (TANs) in the caudate nucleus have sensory response field on the contralateral side (Hikosaka et al. 1989; Shimo and Hikosaka 2001).

By contrast, LLF-type neurons, which are located predominantly in the CM, should exhibit short-latency suppressive responses to the stimulus. This suppression of activity might contribute to disfacilitate striatal neurons. In addition to the short-latency suppression after significant external events, LLF-type neurons also show, in most cases, a subsequent activation that is coincident with the behavioral reaction to the events. The reaction-related activity of the LLF-type neurons must have a different functional role from the short-latency responses to external stimuli. The substantia nigra pars reticulata—Pf—caudate nucleus, and the internal segment of globus pallidus—CM—putamen circuits constitute "internal loops" of the basal ganglia. Thus the reaction-related long latency activity of the CM-Pf complex might encode important information that is being transmitted through these internal loops.

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REFERENCES

ASTON-JOHNS G, RAJKOWSKI J, KUBIAK P, AND ALEXINSKY T. Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *J Neurosci* 14: 4467–4480, 1994.

BOUSSAOUD D AND KERMADI I. The primate striatum: neuronal activity in relation to spatial attention versus motor preparation. *Eur J Neurosci* 9: 2152–2168, 1997.

CASEY BJ, THOMAS KM, WELSH TF, BADGAIYAN RD, ECCARD CH, JENNINGS JR, AND CRONE EA. Dissociation of response conflict, attentional selection, and expectancy with functional magnetic resonance imaging. *Proc Nat Acad Sci USA* 97: 8728–8733, 2000.

COULL JT, FRITH CD, BUCHEL C, AND NOBRE AC. Orienting attention in time: behavioral and neuroanatomical distinction between exogenous and endogenous shifts. *Neuropsychologia* 38: 808–819, 2000.

DE LAS HERAS S, MENGUAL E, AND GIMENEZ-AMAYA JM. Overlapping territories between the thalamostriatal and nigrothalamic projections in cats. *Neuroreport* 9: 275–278, 1998.

DEMPSEY EW AND MORISON RS. The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. *Am J Physiol* 135: 293–300, 1942.

ERIKSEN CW AND HOFFMAN JE. Temporal and spatial characteristics of selective encoding from visual displays. *Percept Psychophys* 12: 201–204, 1972.

ERRO E, LANCIEGO JL, AND GIMENEZ AMAYA JM. Relationships between thalamostriatal neurons and pedunculopontine projections to the thalamus: a neuroanatomical tract-tracing study in the rat. *Exp Brain Res* 127: 162–170, 1999.

GRAYBIEL AM AND BERSON DM. Histochemical identification and afferent connections of subdivisions in the lateralis posterior-pulvinar complex and related thalamic nuclei in the cat. *Neuroscience* 5: 1175–1238, 1980.

GROENEWEGEN HJ AND BERENDSE HW. The specificity of the "nonspecific" midline and intralaminar thalamic nuclei. *Trends Neurosci* 17: 52–57, 1994.

GRUNWERG BS AND KRAUTHAMER GM. Sensory responses of intralaminar thalamic neurons activated by the superior colliculus. *Exp Brain Res* 88: 541–550, 1992.

GUILLERY RW, FEIG SL, AND LOZSADI DA. Paying attention to the thalamic reticular nucleus. *Trends Neurosci* 21: 28–32, 1998.

HARDY H, HEIMER L, SWITZER R, AND WATKINS D. Simultaneous demonstration of horseradish peroxidase and acetylcholinesterase. *Neurosci Lett* 3: 1–5, 1976.

HIKOSAKA O, SAKAMOTO M, AND USUI S. Functional properties of monkey caudate neurons. II. Visual and auditory responses. *J Neurophysiol* 61: 799–813, 1989.

ICHINOHE N AND SHOUMURA K. A di-synaptic projection from the superior colliculus to the head of the caudate nucleus via the centromedian-parafascicular complex in the cat: an anterograde and retrograde labeling study. *Neurosci Res* 32: 295–303, 1998.

JONES EG. Thalamic organization and chemical anatomy. In: *Thalamus, Organization and Function,* edited by Steriade M, Jones EG, and McCormick CD. Amsterdam: Elsevier, 1997, vol. 1, p. 31–174.

KEMP JM AND POWELL TP. The termination of fibres from the cerebral cortex and thalamus upon dendritic spines in the caudate nucleus: a study with the Golgi method. *Philos Trans R Soc Lond B Biol Sci* 262: 429–439, 1971.

KIMURA M. The role of primate putamen neurons in the association of sensory stimulus with movement. *Neurosci Res* 3: 436–443, 1986.

KINOMURA S, LARSSON J, GULYÁS B, AND ROLAND PE. Activation by attention of the human reticular formation and thalamic intralaminar nuclei. *Science* 271: 512–515, 1996.

KROUT KE, LOEWY AD, WESTBY GW, AND REDGRAVE P. Superior colliculus projections to midline and intralaminar thalamic nuclei of the rat. *J Comp Neurol* 431: 198–216, 2001.

KUSAMA T AND MABUCHI M. *Stereotaxic Atlas of the Brain of Macaca fuscata.* Tokyo: University of Tokyo, 1970.

LAPPER S AND BOLAM JP. Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat. *Neuroscience* 51: 533–545, 1992.

MATSUMOTO N, MINAMIMOTO T, GRAYBIEL AM, AND KIMURA M. Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events. *J Neurophysiol* 85: 960–976, 2001.

MCALONAN K, BROWN VJ, AND BOWMAN EM. Thalamic reticular nucleus activation reflects attentional gating during classical conditioning. *J Neurosci* 20: 8897–8901, 2000.

OREM J, SCHLAG-RAY M, AND SCHLAG J. Unilateral visual neglect and thalamic intralaminar lesions in the cat. *Exp Neurol* 40: 784–797, 1973.

PARÉ D, SMITH Y, PARENT A, AND STERIADE M. Projections of brainstem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. *Neuroscience* 25: 69–86, 1988.

PARENT A, PARÉ D, SMITH Y, AND STERIADE M. Basal forebrain cholinergic and noncholinergic projections to the thalamus and brain stem in cats and monkeys. *J Comp Neurol* 277: 281–301, 1988.

PETERSEN SE, ROBINSON DL, AND CURRIE JN. Influences of lesions of parietal cortex on visual spatial attention in humans. *Exp Brain Res* 76: 267–280, 1989.

PETERSEN SE, ROBINSON DL, AND MORRIS JD. The contribution of the pulvinar to visual spatial attention. *Neuropsychologia* 25: 97–105, 1987.

POSNER MI. Orienting of attention. *Q J Exp Psychol* 32: 3–25, 1980.

POSNER MI. Structres and functions of selective attention. In: *Master Lectures in Clinical Neuropsychology*, edited by Boll T and Bryant B. Washington, DC: Am. Psycol. Assoc., 1988, p. 173–202.

POSNER MI. The attention system of the human brain. *Annu Rev Neurosci* 13: 25–42, 1990.

POSNER MI AND DRIVER J. The neurobiology of selective attention. *Curr Opin Neurobiol* 2: 165–169, 1992.

POSNER MI, SNYDER CR, AND DAVIDSON BJ. Attention and the detection of signals. *J Exp Psychol* 109: 160–174, 1980.

POSNER MI, WALKER JA, FRIEDRICH FJ, AND RAFAL RD. Effects of parietal injury on covert orienting of attention. *J Neurosci* 4: 1863–1874, 1984.

POSNER MI, WALKER JA, FRIEDRICH FA, AND RAFAL RD. How do the parietal lobes direct covert attention? *Neuropsychologia* 25: 135–145, 1987.

RAFAL RD AND POSNER MI. Deficits in human visual spatial attention following thalamic lesions. *Proc Natl Acad Sci USA* 84: 7349–7353, 1987.

RAVIZZA SM AND IVRY RB. Comparison of the basal ganglia and cerebellum in shifting attention. *J Cognit Neurosci* 13: 285–297, 2001.

ROBINSON DL, BOWMAN EM, AND KERTZMAN C. Covert orienting of attention in macaques. II. Contributions of parietal cortex. *J Neurophysiol* 74: 698–712, 1995.

ROBINSON DL AND KERTZMAN C. Covert orienting of attention in macaques. III. Contributions of the superior colliculus. *J Neurophysiol* 74: 713–721, 1995.

ROSEN AC, RAO SM, CAFFARRA P, SCAGLIONI A, BOBHOLZ JA, WOODLEY SJ, HAMMEKE TA, CUNNINGHAM JM, PRIETO TE, AND BINDER JR. Neural basis of endogenous and exogenous spatial orienting. A functional MRI study. *J Cognit Neurosci* 11: 135–152, 1999.

ROYCE GJ, BROMLEY S, AND GRACCO C. Subcortical projections to the centromedian and parafascicular thalamic nuclei in the cat. *J Comp Neurol* 306: 129–155, 1991.

SADIKOT AF, PARENT A, AND FRANÇOIS C. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections. *J Comp Neurol* 315: 137–159, 1992a.

SADIKOT AF, PARENT A, SMITH Y, AND BOLAM JP. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneiety. *J Comp Neurol* 320: 228–242, 1992b.

SCHLAG J AND SCHLAG-REY M. Visuomotor functions of central thalamus in monkey. II. Unit activity related to visual events, targeting, and fixation. *J Neurophysiol* 51: 1175–1195, 1984.

SHIMO Y AND HIKOSAKA O. Role of tonically active neurons in primate caudate in reward-oriented saccadic eye movement. *J Neurosci* 21: 7804–7814, 2001.

SIDIBÉ M, BEVAN MD, BOLAM JP, AND SMITH Y. Efferent connections of the internal globus pallidus in the squirrel monkey. I. Topography and synaptic organization of the pallidothalamic projection. *J Comp Neurol* 382: 323–347, 1997.

SIDIBÉ M AND SMITH Y. Thalamic inputs to striatal interneurons in monkeys: synaptic organization and co-localization of calcium binding proteins. *Neuroscience* 89: 1189–1208, 1999.

STERIADE M, DATTA S, PARÉ D, OAKSON G, AND CURRO DOSSI RC. Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *J Neurosci* 10: 2541–2559, 1990.

STERIADE M, DOMICH L, AND OAKSON G. Reticularis thalami neurons revisited: activity changes during shifts in states of vigilance. *J Neurosci* 6: 68–81, 1986.

STERIADE M, JONES EG, AND MCCORMICK CD. Thalamic organization and chemical anatomy. In: *Thalamus. Organization and Function*, edited by Steriade M, Jones EG, and McCormick CD. Amsterdam: Elsevier, 1997, vol. 1, p. 31–174.

STERIADE M, PARENT A, AND HADA J. Thalamic projections of nucleus reticularis thalami of cat: a study using retrograde transport of horseradish peroxidase and fluorescent tracers. *J Comp Neurol* 229: 531–547, 1984.

TEICHER MH, ANDERSON CM, POLCARI A, GLOD CA, MAAS LC, AND RENSHAW PF. Functional deficits in basal ganglia of children with attention-deficit/hyperactivitydisorder shown with functional magnetic resonance imaging relaxometry. *Nat Med* 6: 470–473, 2000.

VERTES RP AND MARTIN GF. Autoradiographic analysis of ascending projections from the pontine and mesencephalic reticular formation and the median raphe nucleus in the rat. *J Comp Neurol* 275: 511–541, 1988.

VITEK JL, ASHE J, DELONG MR, AND KANEOKE Y. Microstimulation of primate motor thalamus: somatotopic organization and differential distribution of evoked motor responses among subnuclei. *J Neurophysiol* 75: 2486–2495, 1996.

WALLACE MT, WILKINSON LK, AND STEIN BE. Representation and integration of multiple sensory inputs in primate superior colliculus. *J Neurophysiol* 76: 1246–1266, 1996.

WATSON RT AND HEILMAN KM. Thalamic neglect. *Neurology* 29: 690–694, 1979.

WEESE GD, PHILLIPS JM, AND BROWN VJ. Attentional orienting is impaired by unilateral lesions of the thalamic reticular nucleus in the rat. *J Neurosci* 19: 10135–10139, 1999.

YINGLING CD AND SKINNER JE. Selective regulation of thalamic sensory relay nuclei by nucleus reticularis thalami. *Electroencephalogr Clin Neurophysiol* 41: 476–482, 1976.